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| 10/018,453 | 10/30/2001 | Marc Zabeau | 29314/35410A | 1637 |

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Nabeela R McMillian
Marshall Gerstein & Borun
6300 Sears Tower
233 South Wacker Drive
Chicago, IL 60606-6402

| EXAMINER |
|---|
| CHAKRABARTI, ARUN K |

| ART UNIT | PAPER NUMBER |
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Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 10/018,453 | Zabeau |
| **Examiner** | **Art Unit** |
| Arun Chakrabarti | 1634 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Feb 7, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *57-103* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *57-103* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. *10/018,453* .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

## DETAILED ACTION

### *Specification*

1. Claims 61-66 are objected to because of the following informalities: Claim 61 is dependent on canceled and therefore nonexistent claim 4. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

2. Claims 92-95, 97-99, 101, and 103 provide for the use of a method for identification of the various allele sequences of a certain region/gene, the scoring of disease-associated mutations, the detection of somatic variations, or studies in the field of molecular evolution, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 92-95, 97-99, 101, and 103 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 61-66 and 84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 61 is dependent on non-existing claim 4. It is not clear what invention is encompassed by claim 61. The metes and bounds of the claims are vague and indefinite.

Regarding claim 84, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

***Claim Rejections - 35 USC § 102***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 57-71, 73-80, 82-83, 85-91, and 96 are rejected under 35 U.S.C. 102(b) as being anticipated by Monforte et al. (PCT International Publication Number WO 97/33000) (September 12, 1997).

Monforte et al teach a method for sequence analysis of one or more target nucleic acids present in one or more biological samples (Abstract), the method comprising the steps of :

a) deriving from one or more biological samples the one or more target nucleic acids (Figures 2-13);

b) subjecting the one or more target nucleic acids obtained from step (a) to a set of separate base-specific, sequence-specific or site-specific complementary cleavage reactions, wherein each cleavage reaction (Figures 2-13);

c) analyzing the sets of non-ordered fragments obtained from step(b) by mass spectrometry (Figures 2-13); and,

d) performing a systematic computational analysis on the mass spectra obtained from step c) to analyze the sequence of the target nucleic acid, wherein the complementary cleavage reactions refer to target nucleic acid digestion characterized by varying specificity and/or to digestion of alternative forms of the target sequence (Page 21, line 1 to page 22, line 24, and Example 11, and Figures 14-17).

Monforte et al teach a method, wherein the one or more biological samples are derived from organism selected from eukaryotes (Page 16, lines 29-30).

Monforte et al teach a method, wherein the one or more target nucleic acids are selected from single stranded DNA, double stranded DNA, single stranded RNA, double stranded RNA, DNA/RNA hybrid (Figures 2-13 and Page 32, line 25 to page 36, line 32).

Monforte et al teach a method, wherein one or more target nucleic acids are derived by one or more consecutive amplification procedures selected from PCR (Page 6, lines 1-10, and Column 17, lines 6-8 and Figure 2).

Monforte et al teach a method, wherein the derived target nucleic acid incorporates one or more nucleosides that are modified on the base, the sugar, and/or the phosphate moiety, wherein the modifications alter the mass and/or the length of the cleavage products (Page 26, line 5 to page 28, line 2).

Monforte et al teach a method, wherein the modification is introduced chemically (Page 27, first paragraph).

Monforte et al teach a method, wherein the modification consists of a 2'-deoxy substituent on the nucleoside triphosphates (Figure 4B and Example 4).

Monforte et al teach a method, wherein the modification consists of a methyl group on C5 of the uridine-5'-monophosphate subunits (Example 4) using an alkylating reagent (Figure 4B and Example 4).

Monforte et al teach a method, wherein the one or more targets nucleic acids of step(a) are purified prior to cleavage through immobilization (Example 8, page 56, lines 30-34).

Monforte et al teach a method, wherein the complementary cleavage reactions are selected from enzymatic (endonucleases and exonucleases) and chemical cleavage (alkali) (Figures 2-13 and Examples 5-8).

Monforte et al teach a method, wherein the complementary cleavage reactions are characterized by a mono-nucleotide or di-nucleotide specificity (Figures 2-13 and Examples 5-7).

Monforte et al teach a method, wherein the one or more target nucleic acids are subjected to enzymatic cleavage reaction using RNA endonuclease RNAse-A (Claim 42, and page 33, line 27, and page 37, lines 19-25).

Monforte et al teach a method, wherein the one or more target nucleic acids are mosaic RNA/DNA nucleic acids prepared with mutant polymerase (Example 1).

Monforte et al teach a method, wherein the set of non-ordered fragments of step(b) is additionally purified using an ion exchange beads (Example 10).

Monforte et al teach a method, wherein the set of non-ordered fragments of step(b) is spotted onto a solid support chosen from solid surfaces or plates (Examples 9-10, and Claims 19 and 43 and page 46, lines 13-32).

Monforte et al teach a method, wherein the mass spectrometric analysis of the nucleic acid fragments is performed using MALDI-TOF (Page 6, line 20 to page 9, line 32 and Example 11 and Figures 1-17).

Monforte et al teach a method, wherein the reference nucleic acid sequence is known and comprises an additional step wherein the one or more mass spectra of the non-ordered fragments obtained in step c) are compared with the known or predicted mass spectra for a reference nucleic acid sequence, and deducing therefrom, by systematic computational analysis, all or part of the nucleotide sequence of the one or more target nucleic acids, and comparing the deduced nucleic acid sequence with the reference nucleic acid to determine whether the one or more target nucleic

acids have the same sequence or a different sequence from the reference nucleic acid (Figures 10-18).

Monforte et al teach a method, wherein the nucleic acid sequence difference that is determined is a deletion, substitution, insertions or combinations thereof (Figures 10-11).

Monforte et al teach a method, wherein the nucleic acid sequence difference is a Single Nucleotide Polymorphism (SNP) (Figures 3, 4A-B, and 10A and page 27, line 10 to page 28, line 2).

7. Claims 100-103 are rejected under 35 U.S.C. 102(b) as being anticipated by New England BioLabs Catalog (Product Number # 203S and 203L, Page 74, 1996-1997).

New England BioLabs Catalog teaches a kit comprising:

a) one or more nucleotide triphosphates (Reaction buffer and Unit assay Conditions Section); b) one or more polymerases; c) one or more nucleic acid cleaving agents (Page 74, T4 DNA polymerase inherently have 3'-5' exonuclease activity as described in Description Section); and d) one or more sets of reference nucleic acids for which the nucleic acid sequence is known (Reaction buffer and Unit assay Conditions Section); e) optionally, reagents to purify the target nucleic acid (Reaction buffer and Unit assay Conditions Section).

New England BioLabs Catalog inherently teaches the use of a kit for analyzing the sequence of known and unknown sequences present in one or more biological samples (Applications Section).

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 72 is rejected under 35 U.S.C. 103(a) over Monforte et al. (PCT International Publication Number WO 97/33000) (September 12, 1997) in view of Geysen et al. (U.S. Patent 6,475,807 B1) (November 5, 2002).

Monforte et al teach the method of claims 57-71, 73-80, 82-83, 85-91, and 96 as described above.

Monforte et al do not teach the method, wherein the modification consists of nucleotides that incorporate alternative isotopes.

Geysen et al. teach the method, wherein the modification consists of nucleotides that incorporate alternative isotopes (Column 9, lines 29-59, and Examples 1-27).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the modification consisting of nucleotides that incorporate alternative isotopes of Geysen et al. in the method of Monforte et al. since Geysen et al. state, "If a nitrogen atom in such molecule having an atomic weight of 14 (N 14) is replaced by isotope N 15, then the MS peak will shift to the right precisely one unit to 306. Furthermore, such isotopic doping will not affect the ionization or chemical reactivity of the molecule. The ability to measure both of the properties of mass and ionic intensity with reasonable accuracy (i.e., mass to about 0.1 atomic mass units and relative intensity to about 3%) provides the basis for a novel encoding strategy using isotopes to isotopically, rather than chemically, encode a monomer to read a synthetic history, instead of tagging a molecule itself. Using the methods of the invention, encoding strategies are devised from the use of the mass information alone, the relative intensity information in two or more mass peaks alone or a combination of the two. The basic methodology of the invention, which is to insert different isotopes into combinatorial constructs to identify addition of monomers or chemical conditions, gives rise to several alternative embodiments for encoding and decoding, which are capable of individual implementation or in selected combinations (Column 9, lines 36-55) ." An ordinary practitioner would have been motivated to combine and substitute the modification consisting of nucleotides that incorporate alternative isotopes of Geysen et al. in the method of Monforte et al., in order to achieve the express advantage, as noted by Geysen et al, of the assays of the invention which has the ability to measure both of the properties of mass and ionic intensity with reasonable accuracy (i.e., mass to

about 0.1 atomic mass units and relative intensity to about 3%) thus providing the basis for a novel encoding strategy using isotopes to isotopically, rather than chemically, encode a monomer to read a synthetic history, instead of tagging a molecule itself and new encoding strategies from the use of the mass information alone, the relative intensity information in two or more mass peaks alone or a combination of the two, which gives rise to several alternative embodiments for encoding and decoding, which are capable of individual implementation or in selected combinations.

10. Claim 81 is rejected under 35 U.S.C. 103(a) over Monforte et al. (PCT International Publication Number WO 97/33000) (September 12, 1997) in view of Hanna (U.S. Patent 6,107,039) (August 22, 2000).

Monforte et al teach the method of claims 57-71, 73-80, 82-83, 85-91, and 96 as described above.

Monforte et al do not teach the method, wherein the cleavage reactions are performed with the nuclease P1.

Hanna teaches the method, wherein the cleavage reactions are performed with the nuclease P1 (Column 24, lines 5-11).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method, wherein the cleavage reactions are performed with the nuclease P1 of Hanna in the method of Monforte et al. since Hanna states, "Substitution of the exonuclease SVP with an endonuclease Nuclease P1 resulted in complete

digestion (Column 24, lines 5-6) ." An ordinary practitioner would have been motivated to combine and substitute the method, wherein the cleavage reactions are performed with the nuclease P1 of Hanna in the method of Monforte et al., in order to achieve the express advantage, as noted by Hanna, of the substitution of the exonuclease SVP with an endonuclease Nuclease P1 that resulted in complete digestion.

11. Claim 84 is rejected under 35 U.S.C. 103(a) over Monforte et al. (PCT International Publication Number WO 97/33000) (September 12, 1997) in view of New England BioLabs Catalog (Product Numbers # 251L and 207L, Page 75, 1996-1997).

Monforte et al teach the method of claims 57-71, 73-80, 82-83, 85-91, and 96 as described above.

Monforte et al do not teach the method, wherein the one or more target nucleic acids are RNA/DNA transcripts that incorporate either dCMP, dUMP or dTMP, prepared with mutant T7 or SP6 polymerase.

New England BioLabs Catalog teaches the method, wherein the one or more target nucleic acids are RNA/DNA transcripts that incorporate either dCMP, dUMP or dTMP, prepared with mutant T7 or SP6 polymerase (Product Numbers # 251L and 207L, Page 75, 1996-1997).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method, wherein the one or more target nucleic acids are RNA/DNA transcripts that incorporate either dCMP, dUMP or dTMP, prepared with mutant T7 or SP6 polymerase of New England BioLabs Catalog in the method of Monforte

et al. since BioLab Catalog states, " RNA produced using the T7 and SP6 RNA polymerases is biologically active as mRNA and can be accurately spliced. Anti-sense RNA produced by reversing the orientation of the cloned DNA insert, has been shown to specifically block mRNA translation in vivo. Labeled single-stranded RNA transcripts of high specific activity are simple to prepare with T7 and SP6 RNA polymerases. Increased levels of detection in nucleic acid hybridization reactions can also be obtained due to the greater stability of RNA-DNA hybrids (Column 1, Page 75, Description section) ." An ordinary practitioner would have been motivated to combine and substitute the method, wherein the one or more target nucleic acids are RNA/DNA transcripts that incorporate either dCMP, dUMP or dTMP, prepared with mutant T7 or SP6 polymerase of New England BioLabs Catalog in the method of Monforte et al.., in order to achieve the express advantage, as noted by BioLab Catalog, of mutant T7 and SP6 RNA polymerases which provides the simple preparation of labeled single-stranded RNA transcripts of high specific activity, increased levels of detection in nucleic acid hybridization, and preparation of biologically active mRNA that can be accurately spliced.

***Conclusion***

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, W. Gary Jones, can be reached on (703) 308-1152.Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

**Arun Chakrabarti**
**Patent Examiner**
**Art Unit 1634**
**January 6, 2003**

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600